Bickerstaff’s Brainstem Encephalitis: A Rare Variant Of The Anti-Gq1b Antibody Syndrome

RAJI SHAMEEM, MD; NIKET SONPAL, MD; MUHAMMAD HAMID, MD; STUART ORSHER, MD; NICKY BHATIA, MD; DAVID M. WAITZMAN, MD, PHD; STEVEN MANDEL, MD

Bickerstaff’s Brainstem Encephalitis (BBE) is a rare neurological condition classically characterized by a constellation of signs and symptoms including acute ophthalmoplegia, ataxia, and altered sensorium. In the 1950’s, Bickerstaff and Cloake described three cases of patients who presented with these clinical features and commented on similarities to the Guillain-Barre Syndrome (GBS), specifically an antecedent upper respiratory or gastrointestinal infection, peripheral neuropathy, and evidence of a albuminocytologic disassociation in the CSF. At about the same time, C. Miller Fisher described cases of ophthalmoplegia and ataxia in a 1956 edition of New England Journal of Medicine. But in contradistinction to BBE, these patients had no change in sensorium and almost universally these patients were areflexic. The majority of patients achieved spontaneous recovery without the need for treatment despite the alarming initial presentation of BBE.

The discovery that a large number of affected patients tested positive for the Anti-Gq1b antibody led to a greater understanding of BBE. Because Anti-Gq1b antibody seropositivity is also seen in other conditions such as GBS and Miller Fisher Syndrome (MFS), many clinicians believe that BBE is not a distinct neurological entity but lies at one end of a spectrum of diseases known as the Anti-Gq1b syndromes. In this article we review some of the key features of BBE including pathophysiology, epidemiology, presentation and investigations, differential diagnosis, and management and treatment.

PATHOPHYSIOLOGY

BBE can occur without any preceding symptoms, but the majority of cases see a preceding infectious illness. Infection as a precipitant for neurological disease has been largely accepted for both GBS and MFS. In a review of 194 cases of Anti-Gq1b Syndrome, antecedent illness was seen in 94 percent of patients, with upper respiratory tract infection being most common. For both BBE and MFS, case-control studies have shown an increased prevalence of seropositivity to both Campylobacter jejuni and Haemophilus Influenzae.

The Anti-Gq1b antibody may have a role in the pathophysiology of BBE and MFS, however the absolute underlying pathogenesis has yet to be discovered. Common
seropositivity between these two conditions highlights their pathophysiological and clinical similarities. Anti-Gq1b antibody is one that interacts with the peripheral nerve ganglioside, Gq1b. Intrinsically, Gq1b is predominantly expressed at neuromuscular injections, sensory nerves, and proximal segments of cranial nerves, such as the oculomotor, trochlear, and abducens nerves. Binding at these sites by the Anti-Gq1b antibody can be a potential explanation for presenting symptoms and signs such as ophthalmoplegia and ptosis. Presence of oropharyngeal palsy can also be explained by expression of Gq1b on the glossopharyngeal and vagus nerves. A recent in-vitro study tested for the central pathogenesis of BBE, compared to a peripheral one for MFS. However, there has been no evidence to suggest that the Gq1b ganglioside is expressed in cells in the central nervous system.

EPIDEMIOLOGY

The incidence of BBE is higher in Japan compared to Western nations. The precise incidence and prevalence of BBE in the United States and other Western nations is currently unknown, which can be attributed to the rarity of the disease and confusion and overlap with other Anti-Gq1b antibody syndromes. A recent nationwide survey of patients in Japan with BBE estimated that the annual incidence of BBE is approximately 0.078 per 100,000 individuals.

There is a lack of similar large-scale BBE epidemiological studies in Japan and in the rest of the world. An increased incidence in Japan and other Asian countries is observed in the summer months. The estimated prevalence of MFS in GBS cases in Western populations is one to five percent. As with BBE, a higher number of MFS cases have been seen in Asian nations, with incidence of up to 25 percent in Japan. GBS is much more commonly encountered by physicians, experiencing an incidence of approximately 1.11 cases per 100,000 person-years. The overlap of GBS with BBE and MFS that is not uncommonly encountered may be an indication that BBE and MFS are not as rare as we assume.

PRESENTATION AND CLINICAL INVESTIGATION

Our present day resources bear no clinical guidelines that describe specific diagnostic criteria for BBE. However, most experts agree that the presence of signs and symptoms including acute bilateral ophthalmoplegia, ataxia, and altered sensorium are highly suggestive of the diagnosis. It should be noted not all cases present classically with this triad of features, and absence of one does not rule out the diagnosis. Altered sensorium is a key symptom which helps differentiate BBE from MFS and GBS especially when the diagnosis in unclear.

Figure 1 illustrates both common and differentiating signs and symptoms of BBE, MFS, and GBS. Altered sensorium is variable where patients can present with drowsiness, stupor, or in the most severe cases, coma, which can be seen in up to 20 percent of cases. Altered sensorium is likely secondary to activation of the brain-stem reticular activating system. Ophthalmoplegia in the setting of BBE presents acutely in a symmetric and usually progressive fashion. Ataxia most commonly presents with truncal and limb involvement, however solitary involvement can be seen as well. Ataxia in BBE suggests cerebellar involvement in the pathogenesis, but this has yet to be clarified. BBE can also present with dysarthria and either hyperreflexia or hyporeflexia on examination.

The diagnosis of BBE is largely based on clinical features, though additional studies may aid in making an accurate diagnosis. The most supportive laboratory investigation is positive Anti-Gq1b antibodies, especially in the setting of the appropriate clinical context. Yet it should be noted that negative antibody testing does not preclude the diagnosis: an analysis of 62 cases of BBE with a strict diagnostic criteria of acute symmetrical ophthalmoplegia, altered sensorium, and ataxia, anti-Gq1b antibodies were positive in 66 percent of patients. A study with a larger population over 500 cases also showed anti-Gq1b seropositivity in approximately 68 percent of patients.

Given that BBE, by its name, is due to a central as opposed to a peripheral disease process, abnormal EEG and MRI findings should not be surprising. As with Anti-Gq1b antibodies, these tests are non-specific and cannot rule out the diagnosis of BBE. EEG findings that can be seen include slow-wave activity in the to range, consistent with central nervous system involvement. MRI findings in BBE have not been well described. In BBE MRI brain findings are variable, where imaging can be unremarkable or hypointense foci on T1-weighted images and hyperintense foci on T2-weighted images can be seen. Foci can be seen in the brainstem, which is expected, however thalamic and basal ganglia lesions have been documented as well.

DIFFERENTIAL DIAGNOSIS

The relationship between BBE, MFS, and GBS remains controversial, however as of today the predominating opinion is doubtful that BBE is a separate distinct clinical condition. Table 1 shows common and differentiating diagnostic, laboratory, and imaging findings in Anti-Gq1b antibody variants including BBE. Many clinicians consider both BBE and MFS to be part of the same spectrum with positive Anti-Gq1b antibodies, the Anti-Gq1b antibody syndrome.
The association of BBE with Anti-Gq1b antibody syndrome is supported by infection being the mutual precipitant for a subsequent immune-mediated reaction.4

At times it can be difficult to differentiate BBE from MFS. MFS usually presents with areflexia, consistent with a peripheral pathology.4 Although BBE is considered a central process, absent or decreased reflexes are seen in about 60 percent of cases.9 Other symptoms frequently observed in MFS include ataxia and ophthalmoplegia, both important clinical features of BBE as well. Ptosis, mydriasis, and facial palsy can frequently be seen in both BBE and MFS.4 Anti-Gq1b antibodies are more frequently observed in MFS than in BBE. Anti-Gq1b seropositivity has been witnessed in up to 83 percent of MFS cases9 whereas only about 66 percent of patients with BBE have demonstrated anti-Gq1b seropositivity. At the same time, other studies have suggested that Anti-Gq1b antibody titer values are similar in BBE and MFS.3

Clinical features of BBE can at times overlap with GBS, with the characteristic triad of co-existent symmetrical limb weakness and flaccidity.1 Analysis of GBS cerebrospinal fluid (CSF) has demonstrated a typical albuminocytological dissociation where there is an increase in total protein but a normal cell count in the CSF. Albuminocytological dissociation in the CSF has also been seen in BBE and MFS, 25 percent and 37 percent, respectively.9

Additional examples of Anti-Gq1b syndrome include acute axonal neuropathy and the pharyngeal-cervical-brachial GBS variant. Acute axonal neuropathy is characterized by an acute onset of symmetrical motor weakness, areflexia, and facial and oropharyngeal weakness. Acute axonal neuropathy is also commonly preceded by infection.11 The pharyngeal-cervical-brachial variant by definition purely involves the cervical, brachial, and/or oropharyngeal muscles and is associated with high titers of anti-Gq1b antibody.11 The differential diagnosis for BBE includes not only Anti-Gq1b syndrome variants but also Wernicke’s encephalopathy, vascular disease involving the brain stem, multiple sclerosis, botulism, and brain stem tumors.3,12 A thorough history and physical exam, and MRI brain imaging can effectively rule out these conditions.

**MANAGEMENT AND TREATMENT**

Effective management and treatment of BBE and other variants of Anti-Gq1b syndrome requires prompt recognition and diagnosis. While the majority of patients with BBE and MFS achieve nearly complete recovery, a number of reported cases of recurrence exist.12 Surprisingly, despite alarming presenting symptoms, spontaneous recovery is frequently seen in both BBE and MFS. The majority of documented cases of BBE have shown patients to regain baseline functional status within 6 months of diagnosis.1 There is also a subset of “probable BBE” cases where the diagnosis is not clear because of atypical neurological symptoms and/or negative antibody testing. These patients have been shown to have a delayed onset of recovery for poorly understood reasons.7

Because of frequent spontaneous recovery and rare occurrence, today there is a lack of generalized consensus on the role of specific treatments for BBE. A recent Cochrane review was not able to give any specific recommendations for the treatment of both BBE and MFS because of an apparent lack of randomized trials evaluating treatment in such clinical settings.13 A few case reports have shown plasmapheresis may

---

**TABLE 1: COMPARISON OF BICKESTAFF’S BRAINSTEM ENCEPHALITIS TO MILLER-FISHER SYNDROME AND GUILLAIN-BARRE SYNDROME**

<table>
<thead>
<tr>
<th></th>
<th>BBE</th>
<th>Miller Fisher Syndrome (MFS)</th>
<th>Guillain-Barre Syndrome (GBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>South-East Asia</td>
<td>South-East Asia</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Diagnostic Criteria</strong></td>
<td>Symmetrical ophthalmoplegia, Ataxia, Altered Sensorium</td>
<td>Symmetrical ophthalmoplegia, Ataxia, Areflexia</td>
<td>Areflexia, Acute Ascending symmetrical limb motor weakness, Dysautonomia</td>
</tr>
<tr>
<td><strong>Laboratory Findings</strong></td>
<td>Anti Gq1b Antibody, CSF pleocytosis, CSF Albumino-cytological dissociation</td>
<td>Anti Gq1b Antibody, CSF pleocytosis, CSF Albumino-cytological dissociation</td>
<td>Anti-Gq1b Antibody*, CSF pleocytosis, CSF Albumino-cytological dissociation</td>
</tr>
<tr>
<td><strong>MRI Findings</strong></td>
<td>High T2 signal with little if any enhancement in brainstem and basal ganglia.</td>
<td>Typically MRI Brain findings are unremarkable given the peripheral predilection.</td>
<td>Anterior nerve root thickening and enhancement surrounding the medullary cone extending along the cauda equina.</td>
</tr>
</tbody>
</table>

* Can be seen in GBS, however less common than in BBE and MFS.
hasten recovery in patients presenting with high serum titers of Anti-Gq1b antibody and with severe complications such as coma.14,15 There has been one reported case of a plasmapheresis and immunoglobulin therapy resistant BBE with eventual resolution with Rituximab treatment.16 Rituximab may have a role in the treatment of BBE based on the effect of anti-CD20 on mice models in countering the immune and complement mediated attack on the pre-synaptic terminal by the Anti-Gq1b antibody.16 The potential role of plasmapheresis and Rituximab in the treatment of BBE highlights that Anti-Gq1b antibodies may be a player in the pathogenesis of BBE.

CONCLUSION

Bickerstaff’s Brainstem Encephalitis is a rare neurological condition that many general physicians and even Neurologists will not encounter during their lifetime. This interesting condition has characteristic signs and symptoms including altered sensorium that should be kept in mind in the setting of new onset ataxia. Our understanding of BBE has greatly evolved with the recognition of the role of Anti-Gq1b antibodies in its pathogenesis. Anti-Gq1b antibody seropositivity has also suggested that BBE is most likely part of a spectrum of diseases under the umbrella known as Anti-Gq1b antibody syndrome. The similarities between BBE, MFS, and GBS may often cause confusion in reaching a diagnosis especially in the setting of clinical overlap. Despite improvements in the understanding of BBE, much more work remains to be done. More epidemiological studies of the incidence and prevalence of BBE should be performed in Western nations. There is also a need for randomized controlled trials to evaluate if certain therapeutic agents or procedures may hasten recovery for patients with BBE.